REMARKS

Applicants and their attorney thank the Examiner for the courtesy of the telephonic interview of April 10, 2006, during which the foregoing claim amendments and the outstanding rejections were discussed.

Claims 1-49 were pending in the application. Claims 1, 4, 8, 11, 15, 17, 21, 23, 28, 31-36, 40, 42 and 48 have been amended and claims 5-7, 12-14, 18-20, 25-27, 30, 37-39 and 46-47 have been canceled, without prejudice. Accordingly, upon entry of the amendments presented herein, claims 1-4, 8-11, 15-17, 21-24, 28-29, 31-36, 40-45 and 48-49 will remain pending in the application.

No new matter has been added. Support for the amendments to the claims can be found in the claims and throughout the specification as originally filed. In particular, support for the expression "low dose of 0.01 – 0.1 mg/kg of an anti-TNFα antibody, or antigen-binding portion thereof" can be found at least at page 19, first paragraph, and in particular at lines 11-13; in Table 2 at page 29; and in Figure 5.

Amendments to and cancellation of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and were done solely to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Information Disclosure Statement

Responsive to the Examiner's request, Applicants provide herewith copies of references C1-D4 cited in the Information Disclosure filed on January 18, 2005.

Rejection of Claims 1-6, 8-13, 15-19, 21-26, 28-37, 40-45 and 49 Under 35 U.S.C. 112, Second Paragraph

The Examiner has maintained the rejection of claims 1-6, 8-13, 15-19, 21-26, and 28-31 and has further rejected claims 32-37, 40-45 and 49 under 35 U.S.C. § 112, second paragraph as being "indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention." In particular, the Examiner is of the opinion that these claims "are indefinite in the recitation of a 'low dose' therapy, because the metes and

bounds of the claimed invention are unclear, so that one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention."

Applicants respectfully traverse the foregoing rejection on the grounds that claims 1-6, 8-13, 15-19, 21-26, 28-37, 40-45 and 49 particularly point out and distinctly claim the subject matter which Applicants regard as their invention, as required by 35 U.S.C. § 112, second paragraph. However, in the interest of expediting prosecution and in no way acquiescing to the validity of the Examiner's rejection, the pending claims have been amended to specify that the "low dose" is a dose of ***0.01 – 0.1 mg/kg*** of an anti-TNFα antibody, or antigen-binding portion thereof. Accordingly, the foregoing rejection has been rendered moot and Applicants respectfully request that the rejection of claims 1-6, 8-13, 15-19, 21-26, 28-37, 40-45 and 49 under 35 U.S.C. § 112, second paragraph be reconsidered and withdrawn.

Rejection of Claims 1-4, 8-11, 15-17, 21-24, 28-29 and 31

Under 35 U.S.C. 112, First Paragraph, Enablement

The Examiner has maintained the rejection of claims 1-4, 8-11, 15-17, 21-24, 28-29 and 31 under 35 U.S.C. 112, first paragraph because, according to the Examiner, "the specification, while being enabling for a TNFα inhibitor which is an anti-TNFα antibody, does not reasonably provide enablement for the full breadth of the genus of "TNFα inhibitors." In particular, the Examiner is of the opinion that

> [a]pplicant's arguments have been fully considered but have not been found convincing.
>
> Applicant argues that one of ordinary skilled in the art would recognize based on the teachings in the specification and the knowledge in the art at the time of filing that any compound which inhibits TNFα may be used in a low dosage therapy of the invention.
>
> This is not found persuasive, at least because the instant claims include in their breadth any TNFα inhibitors, including those which are currently not known in the art and for which no "ordinary dosage has been established. Therefore, it is unpredictable whether a dose which is "substantially lower" than one that may be determined to be "ordinary" will also be effective.

> Applicant further argues that the specification discloses "numerous" examples of TNFα inhibitors to support a genus of inhibitors.
>
> This is not found persuasive, because although the specification discloses three examples of TNFα inhibitors, namely D2E7, Remicade and Embrel, they are disclosed to differ markedly in their effect on the microscopic signs of disease in a mouse model of rheumatoid arthritis at a dose of e.g. 0.1 mg/kg (e.g. pages 29-30). In view of this variability, it remains unpredictable how effective other inhibitors of TNFα will be in alleviating microscopic or other symptoms of the disease, in model systems or in disease subjects.
>
> Therefore, the rejection of record is maintained for the reasons of record, as it applies to the amended claims. The rejection of record is incorporated by reference herein, as if reiterated in full.

In the interest of expediting prosecution, and in no way acquiescing to the validity of the Examiner's rejection, the pending claims have been amended to specify that the "low dose" is a dose of ***0.01 – 0.1 mg/kg*** of an ***anti-TNFα antibody, or antigen-binding portion thereof***. In the Final Office Action, the Examiner had indicated that "the specification, while being ***enabling for a TNFα inhibitor which is an anti-TNFα antibody***, does not reasonably provide enablement for the full breadth of the genus of 'TNFα inhibitors'" (emphasis added; see page 5, lines 3-4 of the Final Office Action). Accordingly, the foregoing rejection has been rendered moot and Applicants respectfully request that the rejection of claims 1-4, 8-11, 15-17, 21-24, 28-29 and 31 under 35 U.S.C. § 112, second paragraph be reconsidered and withdrawn.

Notwithstanding the foregoing, Applicants wish to make the following remarks of record. Applicants respectfully traverse this rejection on the grounds that the specification enables claims directed to a method for treating a disorder in which TNFα activity is detrimental comprising administering to a subject an effective amount of a TNFα inhibitor in a low dose, such that the disorder is treated. Applicants submit that the specification also enables claims directed to a low dose method to alleviate symptoms associated with a disorder in which TNFα activity is detrimental, comprising administering a low dose of a TNFα inhibitor to a subject suffering from the disorder, such that the symptoms are treated. Applicants further submit that the specification enables claims directed to a method of sequestering TNFα into complexes in a subject suffering from a disorder in which TNFα activity is detrimental, by administering a low dose of a TNFα inhibitor to the subject.

Section 112 does not require Applicants to describe every equivalent within the scope of the claims so long as the specification provides sufficient teaching for a person of skill in the art to identify additional equivalents ***without undue experimentation*** (In re Wands 8 USPQ2d 1400-1407, 1404 (CAFC, 1988)). The fact that some experimentation is required does not preclude enablement. See *e.g.*, In re Angstadt, 537 F.2d 498, 503. In fact, the Court of Appeals for the Federal Circuit has announced a test for enablement requiring that the general description set forth sufficient detailed guidance that one of ordinary skill in the art would have a reasonable expectation of success in carrying out the claimed invention. See *e.g.*, in re Wright, 999 F.2d 1557 (Fed. Cir. 1993). The fact that some experimentation may be required does not constitute a lack of enablement ***as long as the amount of experimentation is not unduly extensive***. Amgen Inc. v. Chugai Pharmaceutical Co., Ltd., 927 F.2d 1200, 1213 (CAFC 1991). Moreover, "as long as the specification discloses at least one method (emphasis added) for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of §112 is satisfied." In re Fischer, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

Applicants respectfully submit that based on the teachings in Applicants' specification as well as the general knowledge in the art, one of skill in the art would be able to make and use the claimed invention using only routine experimentation.

Specifically, the instant specification teaches several examples of TNFα inhibitors which are suitable for use in the claimed methods, including etanercept, infliximab, human anti-TNFα monoclonal antibodies, CDP 571, and CDP 870 (see page 5, lines 11-14). The specification also contains working examples demonstrating the efficacy of three different TNFα inhibitors, including a chimeric antibody, a human antibody, and a fusion protein, in the claimed methods. As described at page 27, lines 20-26 of the specification, each of the three TNFα inhibitors was administered to mice at doses ranging from 0.01 mg/kg -10 mg/kg, including the doses of 0.01 mg/kg and 0.1 mg/kg. The results demonstrate that mice treated with these various TNFα inhibitors show improvements in their symptoms, including a decrease in joint inflammation and joint vascularity, as well as cartilage and bone erosion. Thus, the examples provided in the specification demonstrate that the claimed low dose methods may be successfully practiced using various TNFα inhibitors.

Moreover, the specification provides sufficient teachings such that a person of skill in the art would be able to identify additional TNFα inhibitors suitable for use in the claimed methods without undue experimentation. The instant specification describes at least in Example 1, at pages 26-30, experiments which can be carried out in a mouse model to evaluate the efficacy of a particular TNFα inhibitor in alleviating arthritic symptoms at the claimed dosage range. In particular, Example 1b teaches evaluation of development of arthritis and Example 1(d) teaches microscopic analysis of vascularity, inflammation, cartilage and bone erosion to evaluate the efficacy of a TNFα inhibitor. One of skill in the art would recognize that these assays taught in the specification may be used to evaluate and identify other TNFα inhibitors useful in the claimed low dose methods. Thus, given the extensive guidelines and working examples provided by Applicants, combined with the high skill level in the art, testing of a given TNFα inhibitor for use in the subject invention would not constitute undue experimentation.

The Examiner has asserted that "although the specification discloses three examples of TNFα inhibitors, namely D2E7, Remicade and Embrel, they are disclosed to differ markedly in their effect on the microscopic signs of disease in a mouse model of rheumatoid arthritis at a dose of e.g. 0.1 mg/kg." Applicants respectfully submit that although the three anti-TNFα inhibitors tested may have exhibited slightly varied responses, these inhibitors were effective in reducing inflammation, vascularity, cartilage erosion and bone erosion at low doses (see Table 2 at page 29 of the specification).

In summary, Applicants respectfully submit that, in view of the ample teachings provided in the specification and the extensive knowledge available in the art, a person of ordinary skill in the art would have been able to make and use claimed methods for treating a disorder or symptoms associated with a disorder in which TNFα activity is detrimental comprising administering to a subject an effective amount of a TNFα inhibitor in a low dose using only routine experimentation.

Rejection of Claims 1-4, 8-11, 15-17, 21-24, 28-29 and 31

Under 35 U.S.C. 112, First Paragraph, Written Description

The Examiner has maintained the rejection of claims 1-4, 8-11, 15-17, 21-24, 28-29 and 31 under 35 U.S.C. 112, first paragraph as "containing subject matter which was not described

in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention." Specifically, the Examiner is of the opinion that "Applicant is not in possession of a method for treating a disorder by administering a 'TNFα inhibitor,' as generically recited in the instant claims" for the reasons of record.

In the interest of expediting prosecution and in no way acquiescing to the validity of the Examiner's rejection, the pending claims have been amended to specify that the "low dose" is a dose of 0.01 – 0.1 mg/kg of ***an anti-TNFα antibody, or antigen-binding portion thereof.*** Accordingly, the foregoing rejection has been rendered moot and Applicants respectfully request that the rejection of claims 1-4, 8-11, 15-17, 21-24, 28-29 and 31 under 35 U.S.C. 112, first paragraph, for lack of written description be reconsidered and withdrawn.

Notwithstanding the foregoing, Applicants wish to make the following remarks of record. Applicants respectfully submit that the instant specification discloses a sufficient number of examples of TNFα inhibitors to support a genus of TNFα inhibitors. It is a well established principle of U.S. Patent Law that "[a] specification may, within the meaning of 35 U.S.C., § 112, First Paragraph, contain a written description of a broadly written claimed invention ***without describing all species that claim encompasses***." Utter v. Hiraga, 845 F.2d 993, 6 USPQ2d 1709 (Fed. Cir. 1988). Moreover, "a 'representative number' is an ***inverse function of the skill and knowledge in the art***. Satisfactory disclosure of a 'representative number' depends on whether one of skill in the art would recognize that the Applicant was in possession of the ***necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed***." (see M.P.E.P. 2163 (II.A.3.a.ii)).

As described above, the instant specification teaches examples of different types of TNFα inhibitors, *e.g.*, anti-TNFα antibodies and fusion proteins containing extracellular domains of a TNFα receptor, and provides working examples of three species of TNFα inhibitors, *e.g.*, etanercept, infliximab and D2E7. The specification further teaches that a TNFα inhibitor may be selected, for example, based on its ability to inhibit TNFα activity in a standard *in vitro* assay such as the L929 neutralization assay (see page 7, line 1 of specification). Further, the relevant skill and knowledge in the art was high at the time of the invention, such that an artisan could easily recognize if an agent inhibits TNFα activity using standard assays known in the art. Moreover, in addition to the specific TNFα inhibitors disclosed in the specification,

various other TNFα inhibitors were well known in the art at the time the invention was filed (see, for example, TNFα inhibitors described in U.S. Patent No. 5,519,000, U.S. Patent No. 6,143,866, U.S. Patent No. 5,654,407 and U.S. Patent No. 6,177,077). Thus, based on the teachings in the specification and the knowledge in the art at the time of the invention, it is Applicants' position that one of skill in the art would reasonably conclude that Applicants were in possession of the claimed invention at the time the application was filed.

Rejection of Claims 1- 49 Under 35 U.S.C. 102(b)

The Examiner has maintained the rejection of claims 1-31 and has further rejected claims 32-49 under 35 U.S.C. 102(b) as lacking novelty in view of U.S. Patent No. 6,258,562 (Salfeld *et al.*; hereinafter "the '562 patent"). The Examiner relies on the '562 patent for teaching compositions and methods of use relating to human anti-TNFα antibodies, including the antibody D2E7. In particular, the Examiner states that the '562 patent teaches "an effective dose of the antibody is 0.1-20 mg/kg."

Applicants respectfully traverse this rejection on the grounds that the '562 patent fails to teach or suggest each and every element of the claimed invention in accordance with 35 U.S.C. §102(b).

The pending claims are directed to a method for treating a disorder in which TNFα activity is detrimental comprising administering to a subject an effective amount of an anti-TNFα antibody, or antigen-binding portion thereof, in a ***low dose of 0.01-0.1mg/kg***, such that the disorder is treated. The pending claims are also directed to a low dose method to alleviate symptoms associated with a disorder in which TNFα activity is detrimental, comprising administering a ***low dose of 0.01-0.1mg/kg*** of an anti-TNFα antibody, or antigen binding portion thereof, to a subject suffering from said disorder, such that the symptoms are treated. The pending claims are further directed to a method of sequestering TNFα into complexes in a subject suffering from a disorder in which TNFα activity is detrimental, by administering a ***low dose of 0.01-0.1mg/kg*** of an anti-TNFα antibody, or antigen binding portion thereof, to the subject.

Under 35 U.S.C. 102, for a prior art reference to anticipate a claimed invention, the prior art must teach *each and every element* of the claimed invention. *Lewmar Marine v. Barient*, 827

F.2d 744, 3 USPQ2d 1766 (Fed. Cir. 1987). Furthermore, "the identical invention must be shown in as complete detail as is contained in the...claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

The pending claims are directed to methods utilizing ***a low dose comprising 0.01-0.1 mg/kg*** of an anti-TNFα antibody, or antigen-binding portion thereof. As acknowledged by the Examiner, the '562 patent teaches that a therapeutically effective dose range for human anti-TNFα antibodies is ***0.1-20 mg/kg***. When considering prior art that teaches a range "touching" the claimed range, the M.P.E.P. provides the following:

> When the prior art discloses a range which ***touches***, overlaps or is within the claimed range, but ***no specific examples falling within the claimed range are disclosed, a case by case determination must be made as to anticipation***. In order to anticipate the claims, the claimed subject matter must be disclosed in the reference with "sufficient specificity to constitute an anticipation under the statute." What constitutes a "sufficient specificity" is fact dependent. ***If the claims are directed to a narrow range, the reference teaches a broad range, and there is evidence of unexpected results within the claimed narrow range,*** depending on the other facts of the case, ***it may be reasonable to conclude that the narrow range is not disclosed with "sufficient specificity" to constitute an anticipation of the claims***. The unexpected results may also render the claims unobvious. (See M.P.E.P. § 2131.03)

In the present case, the '562 patent discloses a dose range (0.1-20 mg/kg) which touches the claimed range (0.01-0.1 mg/kg), but fails to disclose a specific example falling within the claimed range. Moreover, the instant claims are directed to a narrow range of 0.01-0.1 mg/kg, while the '562 patent discloses a much broader range of 0.1-20 mg/kg. Finally, the instant specification discloses the unexpected discovery that a low dose of 0.01-0.1 mg/kg of a TNFα inhibitor, *e.g.*, an anti-TNFα antibody or antigen-binding portion thereof, can be effective in treating the claimed disorders and alleviating symptoms associated with these disorders. Applicants teach in the specification various benefits associated with administering the claimed low doses of a TNFα inhibitor, *e.g.*, an anti-TNFα antibody or antigen-binding portion thereof, including improvement in cartilage erosion (see, for example, Table 2 at page 29 of the specification.) Applicants also teach in the specification that low doses of a TNFα inhibitor, *e.g.*, an anti-TNFα antibody or antigen-binding portion thereof, may be advantageous as they may decrease side effects and may decrease the frequency of administration associated with the

normally prescribed dose (see, for example, page 7, lines 20-22 of the specification). In view of the foregoing, it is evident that the '562 patent fails to teach or suggest the claimed narrow range of 0.01-0.1 mg/kg with sufficient specificity to constitute an anticipation of the claims.

In view of the foregoing, Applicants respectfully request that the rejection of claims 1-49 under 35 U.S.C. 102(b) as lacking novelty over the '562 patent be reconsidered and withdrawn.

Rejection of Claims 1- 49 Under 35 U.S.C. 102(e)

The Examiner has maintained the rejection of claims 1-31 and has further rejected claims 32-49 under 35 U.S.C. 102(e) as lacking novelty in view of U.S. Patent No. 6,509,015 (Salfeld *et al.*; hereinafter "the '015 patent"). The Examiner relies on the '015 patent for teaching compositions and methods of use relating to human anti-TNFα antibodies, including the antibody D2E7. In particular, the Examiner relies on the '015 patent for teaching that "the range of therapeutically effective amount of the antibody of the invention is 0.1-20 mg/kg, a range overlapping with the one instantly claimed."

Applicants respectfully traverse this rejection on the grounds that the '015 Patent fails to teach or suggest each and every element of the claimed invention in accordance with 35 U.S.C. §102(e).

Similar to the '562 patent, the '015 patent fails to anticipate the claimed invention in that there is no teaching or suggestion in the '015 patent to use a low dose ***of 0.01-0.1 mg/kg*** of a TNFα inhibitor. Indeed, there is no teaching or suggestion in the '015 patent to consider any doses which appear less efficacious in standard assays than saturating doses. As discussed above, when "the prior art discloses a range which ***touches***... the claimed range, but ***no specific examples falling within the claimed range are disclosed, a case by case determination must be made as to anticipation***." ***"If the claims are directed to a narrow range, the reference teaches a broad range, and there is evidence of unexpected results within the claimed narrow range,*** depending on the other facts of the case, ***it may be reasonable to conclude that the narrow range is not disclosed with 'sufficient specificity' to constitute an anticipation of the claims***." (See M.P.E.P. § 2131.03)

Similar to the '562 patent, the '015 patent discloses a dose range (0.1-20 mg/kg) which touches the claimed range (0.01-0.1 mg/kg), but fails to disclose a specific example falling within the claimed range. The instant claims are directed to a narrow range of 0.01-0.1 mg/kg,

while the '015 patent discloses a much broader range of 0.1-20 mg/kg. Finally, the instant specification discloses the unexpected discovery that the claimed low dose of 0.01-0.1 mg/kg of a TNFα inhibitor, *e.g.*, an anti-TNFα antibody or antigen-binding portion thereof, can be effective in treating the claimed disorders and alleviating symptoms associated with these disorders. Thus, it is Applicants' position that the '015 patent fails to teach or suggest the claimed narrow range of 0.01-0.1mg/kg with sufficient specificity to constitute an anticipation of the claims.

In view of the foregoing, Applicants respectfully request that this rejection of claims 1-49 under §102(e) over the '015 patent be reconsidered and withdrawn.

Rejection of Claims 1- 49 Under Obviousness-Type Double Patenting

The Examiner has maintained the rejection of claims 1-31 and has further rejected claims 32-49 under the judicially created doctrine of obviousness-type double patenting as being unpatentable in view of claims 1-100 of U.S. Patent No. 6,509,015 (Salfeld *et al.*; hereinafter "the '015 patent"). The Examiner is of the opinion that "[a]lthough the conflicting claims are not identical, they are not patentably distinct from each other for the reasons set forth in the prior Office Action."

Applicants respectfully traverse the aforementioned obviousness-type double patenting rejection on the grounds that the claimed low dose methods would not have been obvious over the claims of the '015 patent.

A nonstatutory basis exists for a double patenting rejection when the claimed invention is an obvious variation of an invention in an issued patent (M.P.E.P. 804(B)(1)). Accordingly, any analysis employed in an obviousness-type double patenting rejection parallels the guidelines for analysis of a 35 U.S.C. 103 obviousness determination. *In re Braat*, 937 F.2d 589, 19 USPQ2d 1289 (Fed. Cir. 1991); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). To establish a *prima facie* case of obviousness, it is necessary for the Examiner to present evidence, preferably in the form of some teaching, suggestion, incentive or inference in the applied references, or in the form of generally available knowledge, that one having ordinary skill in the art would have been ***motivated*** to make the claimed invention and would have had a reasonable ***expectation of success*** in making the claimed invention. Under section 103, "[b]oth the suggestion and the expectation of success must be founded in the prior art, not

in applicant's disclosure" (*Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.* 927 F.2d 1200, 1207, 18 USPQ2d 1016 (Fed. Cir. 1991), quoting *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed Cir. 1988)). Moreover, when considering prior art which "touches" the claimed range, "unexpected results [within the claimed narrow range] may... render the claims unobvious." (See M.P.E.P. §2131.03)

The methods of the invention are unique in that they embody Applicants' unexpected discovery that low doses, *e.g.*, 0.01-0.1 mg/kg, of TNFα inhibitors can be effective in treating the claimed disorders and alleviating symptoms associated with these disorders. Applicants teach in the specification various benefits associated with administering low doses of the TNFα inhibitors, including improvement in cartilage erosion (see, for example, Table 2 at page 29 of the specification). Applicants also teach in the specification that low doses of a TNFα inhibitor may be advantageous as they may decrease side effects and may decrease the frequency of administration associated with the normally prescribed dose (see, for example, page 7, lines 20-22 of the specification).

In contrast, the '015 patent provides general guidance with regard to normally prescribed dosing. The '015 patent fails to teach or suggest methods which use low doses of a TNFα inhibitor, let alone a dose of 0.01-0.1 mg/kg of a TNFα inhibitor. In particular, as acknowledged by the Examiner, the '015 patent teaches that a therapeutically effective dose range for human anti-TNFα antibodies is 0.1-20 mg/kg. Thus, the '015 patent fails to teach or suggest methods which use a ***low dose of 0.01-0.1 mg/kg of a TNFα inhibitor, e.g., an anti-TNFα antibody or antigen-binding portion thereof***. Moreover, one of ordinary skill in the art would not have been motivated to arrive at the claimed invention, *i.e.*, to select the claimed dosage range of 0.01 to 0.1 mg/kg, based on the disclosure of the '015 patent, because the '015 patent already teaches the successful inhibition of human TNFα activity using a dosage range of 0.1-20 mg/kg.

In view of the foregoing, it is evident that the teachings of the '015 patent fail to render the claimed invention obvious. In addition, while the '015 patent discloses a dose range which "touches" the claimed dose range of 0.01-0.1 mg/kg, the unexpected results provided by Applicants further prove that the pending claims are unobvious over the '015 patent. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this obviousness-type double patenting rejection of claims 1-49.

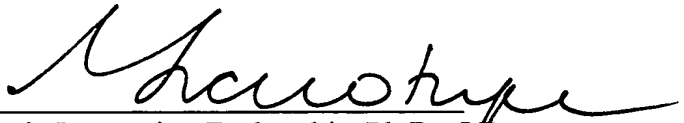
CONCLUSION

Reconsideration and allowance of all the pending claims is respectfully requested. If a telephone conversation with Applicants' Attorney would help expedite the prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

In addition, Applicants include herewith authorization to charge fees associated with new claims and the extension of time with which to respond, to Deposit Account No. 12-0080, under Order No. BBI-190RCE. The Director is also hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to Deposit Account No. 12-0080, under Order No. BBI-190RCE.

Dated: **April 14, 2006**

Respectfully submitted,



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